Chapter 7

Women with early rheumatoid arthritis have more disease activity and use more antirheumatic therapy compared with men, but have similar joint damage after 5 years

Jennie Ursum
Naomi B Klarenbeek
Maarten Boers
Ben AC Dijkmans
Tom WJ Huizinga
Cornelia F Allaart
Dirkjan van Schaardenburg

Submitted for publication

Abstract

Objective. To determine whether there are sex differences in patients with early rheumatoid arthritis (RA) concerning disease activity, functional status, radiographic damage and the use of medication.

Methods. In patients from the early arthritis clinic of the Jan van Breemen Institute (EAC-JBI), who fulfilled the 1987 ACR-criteria for RA at baseline and had 5 years follow-up, the disease activity score (DAS), functional status (health assessment questionnaire, HAQ) and annual radiographic progression rate were compared between women and men, corrected for potential confounders. The same analysis was performed on the 5-year data of the two initial monotherapy groups of the BeSt trial in early RA.

Results. Women were younger than men (mean(sd) 55(14) vs. 58(14) years, p=0.01 in EAC-JBI; 53(13) vs. 57(13), p=0.05 in BeSt). Women reported higher pain levels than men and had a higher mean DAS. In the EAC-JBI, the mean HAQ was higher in women. The annual radiographic progression of women and men was similar in both cohorts. These results did not change after correction for potential confounders. The median (interquartile range) number of used DMARDs was higher in women than in men (2(1-3) vs.1(1-2), p=0.02 in EAC-JBI; 3(2-4) vs. 2(1-4), p=0.007 in BeSt).

Conclusion. Women with early RA have a higher disease activity score, more functional impairment and receive more medication than men, whereas the radiographic progression rate is similar between the sexes. Women experience a higher burden of disease. The fact that women receive more medication may offset a possibly more severe disease course in women.

Introduction

The effect of sex on the incidence and course of rheumatoid arthritis (RA) is complex. The incidence of RA is higher in women than in men at younger ages,[1,2] resulting in more women being affected, with a younger mean age. There is debate about whether female sex is a marker of a more severe disease course.[2-5] Disease severity is often measured using disease activity as a process marker, and functional status or radiographic damage as an outcome marker. When assessing these domains, the intensity of antirheumatic therapy should also be taken into account, since this has become a powerful prognostic factor.[6,7]

Disease activity is often measured by the disease activity score based on 28 joints (DAS28).[8] This score is composed of both objective and disease-perception parameters. The swollen joint count (SJC) and the erythrocyte sedimentation rate (ESR) are objective elements. In men compared with women, both higher, lower and similar mean baseline SJC values have been reported.[5,9-11] Women on average have a higher ESR compared with men, and for both sex values increase with age,[12] although ESR increases more progressively with age in men.[13] The other two components of the DAS28, tender joint count (TJC) and visual analogue scale of general health (VASGH), are elements of disease-perception, mostly reported to be higher in women.[5,10,14,15] Pain perception is affected by sex: healthy females exhibit a significantly lower mean pressure pain threshold.[16-18] Several cross-sectional studies found a higher mean DAS in women compared with men, both in early and established RA,[5,11,15,19-21] with one exception of a similar DAS between men and women.[14]

Functional status is mostly reported to be worse for women compared with men. In (early) RA patients a higher total health assessment questionnaire (HAQ)[22,23] score in women during up to eight years was reported.[5,11,14,15,20,24] Differences between sex in HAQ scores should be interpreted with caution, however, since men intend to overestimate their functional abilities.[25] Additionally, the aforementioned higher pain pressure threshold in men[17,26] and their greater muscle strength has a major impact on physical function.[27]

Because RA starts at a younger age in females, this results in a longer average exposure to inflammation compared with males of the same age,[2,28] with possibly more radiographic damage. Whether the female sex truly is a prognostic factor for radiographic damage is not clear. There are reports of more frequent erosive disease in men than in women[29] as well as of more in women than in men,[30-32] but most studies have found a similar radiographic progression rate for females and males.[5,15,20,33-35]

Since women have a higher disease activity than men, women might also need more intense treatment. Indeed, one study showed that women switched disease modifying anti-rheumatic drugs (DMARD) more frequently during the first year compared with men[20], and in the

Norwegian NOR-DMARD study the average number of DMARDS was higher in women compared with men.[2]

In conclusion, it is not yet clear whether women have a more severe disease course compared with men. Apparent differences in disease activity between the sexes may be caused by differences in physiology as is seen in the ESR, or by a difference in pain perception. Measurements of functional status by questionnaires may be hampered by different physical activity patterns between the sexes. Radiologic damage would thus seem to be the best parameter to determine any difference in outcome between the sexes, but such a comparison needs to take possible differences in therapy into account. The aim of the present study is to determine whether there are sex differences concerning disease activity, functional status, radiographic damage and the use of antirheumatic medication in two cohorts of patients with early RA.

Patients and Methods

Patients

The first cohort consisted of patients with early arthritis, who were included in the Early Arthritis Cohort (EAC) of the Jan van Breemen Institute. Since 1995, this cohort includes all new patients of 18 years and older with arthritis of two or more peripheral joints and less than three years symptom duration. Exclusion criteria are prior treatment with DMARDs and a diagnosis of crystal synovitis, osteoarthritis or spondylarthropathy. For the present study all patients were selected who fulfilled the 1987 ACR criteria for RA[36] at baseline. Annual follow-up data up from a minimum of a baseline visit to a maximum of five years were used from the period 1995-2007. Treatment of these patients was generally with initial monotherapy, according to the opinion of the rheumatologist.

The second cohort comprised the two initial monotherapy groups of the BeSt study: sequential monotherapy and step-up combination therapy. The BeSt study is a multicenter randomized trial of four different treatment strategies in patients with early active RA of less than two years duration.[37] The two other arms of the BeSt study consisted of initial combination therapy, and therefore were considered unfit for comparison with the patients of the EAC-JBI. The inclusion period of the BeSt study was 2000-2002. Thirty-four patients of the JBI-EAC participated in the BeSt trial and were assigned only to the BeSt cohort for the present study. Treatment in the BeSt study was dictated by protocol, and changes in therapy could be made at three-monthly assessments. The next treatment step was made if the disease activity score (DAS, 44 joint score) 38 was more than 2.4. For both cohort studies the

local ethics committee approved the study protocol, and all patients gave their written informed consent.

Patient characteristics

In both cohorts, the following patient characteristics were collected at baseline: demographic data, symptom duration, bodymass index (BMI), tender and swollen joint count, laboratory values disease activity score based on 28 joints (DAS28)[8] or on 44 joints, functional status assessed with the Dutch version of the Health Assessment Questionnaire [HAQ]22,23. The use of DMARDs was collected from chart review. During follow-up the DAS and HAQ were performed three-monthly in the BeSt study; in the EAC-JBI three-monthly in the first year, six-monthly in the second year and annually thereafter. And the radiographic damage on annual radiographs of hands and feet was assessed with the Sharp/Van der Heijde Score (SHS).39 In the EAC-JBI two experienced rheumatologists, who were blinded to the other variables, with an interreader intraclass correlation coefficient (ICC) of 0.95, each performed part of the scoring, with known time sequence. In the BeSt study, annual radiographs of baseline and year 1-2-3-4-5 were scored in one session per patient by two independent readers, blinded to treatment allocation, patient identity and in random time sequence. Mean score of the two readers was used in the analysis. The interreader ICC for the year 0 to year 5 interval was 0.98.

Analysis

Baseline characteristics were compared between males and females using Student's t-test, Mann-Whitney U test or the chi square test, as appropriate. In order to take the varying length of follow-up in the EAC-JBI into account, for the outcome measures DAS and HAQ the area under the curve (AUC) was calculated and divided by the total time of follow-up (AUC-DAS, AUC-HAQ). The annual progression rate of the radiographic damage was determined by performing a linear regression for each patient, in this way the varying length of follow-up was taken into account. The same analysis was used for the 5-year data of the two initial monotherapy groups of the BeSt study.

Linear regression was used to assess the association between sex (women were coded '1' men were coded '0') and the outcomes AUC-DAS and the natural logarithm of AUC-HAQ (to approach normality), corrected for follow-up duration, potential confounders at baseline and the number of used DMARDs. The beta's of the AUC-HAQ were back-transformed as displayed in the results. Logistic regression analysis was performed to assess the association between sex (women coded '1' and men '0')and the radiographic status (dichotomised in no (0) progression or a progression rate >0), again corrected for potential confounders and the number of used DMARDs.

First sex was added to the models. Then, baseline characteristics were added one by one and if it caused >10% change in the beta of the variable sex it was classified as a confounder. Then, a multivariable model was built by adding the identified confounders in order to retrieve the best model. This was performed for each outcome measure (DAS_AUC, HAQ-AUC, radiographic progression rate).

Results

Characteristics EAC-JBI cohort

680 patients from the EAC-JBI were included, 69% were female. At baseline women on average were a few years younger, had more tender joints, and less swollen joints compared with men (table 1). Women on average had a worse general health and more pain. Disease activity was higher and functional status worse in women compared with men. Of the laboratory measurements only CRP was higher in men. DMARDs used by the patients in descending order of frequency and sometimes in combinations were (% women vs. % men): methotrexate (72 vs. 65%), sulphasalazine (45 vs. 40%), prednisone (26% vs 27%) hydroxychloroquine (24 vs. 15%), infliximab (7 vs. 3%), leflunomide (6 vs. 4%), ciclosporine (4 vs. 2%), adalumimab (4 vs. 2%), etanercept (3 vs. 3 %), intramuscular gold (3 vs. 2%), azathioprine (2 vs. 2 %), cyclosphosphamide and rituximab (both <1% in women and men). 216 patients completed five years of follow-up (32%). The mean follow-up duration was 2.9 years (SD 1.8). The percentage females remained 70% during follow-up. The reasons for patients not reaching five years follow-up (n=464) were: included less than five years before n=216 (32%), remission n=20 (3%), changed diagnosis n=7 (1%), moved n=34 (5%), deceased n=27 (4%), patient´s choice to not longer visit the research nurse n=106 (16%), lost to follow-up n= 54 (8%).

Characteristics BeSt

In total, 247 patients were randomized to treatment groups 1 and 2 of the BeSt study, of whom 70% were female. As in the EAC-JBI, women were younger than men at inclusion, had a higher disease activity score with more tender joints, a higher VAS general health, and a higher HAQ score (table 1). In contrast to the EAC-JBI, the number of swollen joints, VAS pain and CRP was not significantly different between men and women. In addition, symptom duration tended to be shorter and the proportion of patients with antibodies to citrullinated proteins or peptides (ACPA) and IgM rheumatoid factor (IgM-RF) tended to be lower among females in BeSt. The type and amount of DMARDs used by the patients in the BeSt study were described earlier.40

205 patients completed five years of follow-up (83%). The withdrawals did not influence the sex distribution. Patients terminated the study earlier due to the following reasons: patient's choice n=23 (9%), deceased n=6 (2%), changed diagnosis n=5 (2%), other reasons n=8 (3%).

Table 1. Baseline characteristics of women and men in two cohorts of early RA

	EAC-JBI			BeSt		
Characteristics at baseline	**Female** (n=464)	**Male** (n=215)	**P**	**Female** (n=172)	**Male** (n=75)	**P**
Age, years[a]	55 (14)	58 (14)	0.01	53 (13)	57 (13)	0.03
Symptom duration[c]	20 (11-31)	19 (11-31)	ns	29 (15 – 56)	20 (12 – 39)	ns
BMI	26 (5)	26 (4)	ns	26 (5)	26 (3)	ns
TJC28[c]	7 (3-10)	4 (2-8)	<0.01	12 (7 – 17)	11 (7 – 17)	ns
Ritchie Articlular Index	-	-	-	15 (10 - 20)	12 (9 – 16)	<0.01
SJC28[c]	8 (5-12)	9 (5-14)	0.05	10 (7 – 15)	11 (8 – 15)	ns
SJC44	-	-	-	13 (10 – 20)	15 (10 – 18)	ns
VAS general health, mm[a]	57 (23)	51 (25)	0.01	54 (19)	48 (20)	0.02
Laboratory values						
ESR, mm/1st hour[c]	26 (15-44)	31 (16-46)	ns	40 (23 – 58)	33 (18 – 55)	ns
CRP, mg/L[b]	16 (3)	22 (3)	0.01	20 (8 – 50)	26 (9 – 68)	ns
IgM-RF positivity, %	51	53	ns	62	73	ns
ACPA positivity, %	57	60	ns	56	68	ns
Disease activity						
DAS28[a]	5.32 (1.18)	4.98 (1.17)	<0.01	6.12 (0.95)	5.79 (0.96)	0.05
DAS44	-	-	-	4.62 (0.90)	4.26 (0.70)	<0.01
Functional status HAQ[a]	1.30 (0.75)	1.09 (0.74)	<0.01	1.48 (0.65)	1.23 (0.60)	<0.01
Radiograpic damage SHS[c]	0 (0-2)	0 (0-4)	ns	4.0 (1.5 – 8.0)	5.0 (1.5 – 10.0)	ns

a) Mean (sd); b) Back transformed mean (sd); c) Median (IQR); ns = not significant.
BMI= Body Mass Index , TJS = tender joint count based on 28 or 44 joints, SJC = swollen joint count based on 28 or 44 joints, VAS = visual analogue scale, ESR= erythrocyte sedimentation rate, CRP = C-reactive protein, IgM-RF= IgM rheumatoid factor, ACPA= antibodies to citrullinated proteins or peptides, DAS = disease activity score, HAQ= health assessment questionnaire, SHS= Sharp-van der Heijde score.

Outcome measures

In both cohorts the AUC-DAS in women was higher compared with men (DAS28 difference 0.42 in EAC-JBI and DAS44 difference 0.30 in BeSt (p=0.01); Table 2). The HAQ was significantly higher in women than in men of the EAC-JBI (0.72 versus 0.49; p<0.01); in BeSt the median AUC-HAQ was comparable for women and men. In both cohorts there was no statistically significant difference in the annual radiographic progression between women and men, although in BeSt there was a trend for a higher radiographic progression rate in men.

The median number of DMARDs was higher in women than in men in both cohorts: 2 versus 1 (p=0.02) in EAC-JBI en 3 versus 2 in BeSt (p<0.01).

Table 2. Characteristics during follow-up of women and men in two early RA cohorts

	EAC-JBI (Follow-up duration up to 5 years)			**BeSt study** (All patients 5 years follow-up)		
	Women n=464	**Men** n=215	**P[1]**	**Women** n=173	**Men** n=74	**P[2]**
DAS28[†]	3.69 (1.31)	3.27 (1.48)	<0.01	-	-	-
DAS44[†]	-	-	-	2.32 (0.78)	2.02 0.80)	<0.01
HAQ[‡]	0.72 (0.22-1.16)	0.49 (0.30-1.00)	<0.01	0.58 (0.25-0.99)	0.60 (0.29-1.03)	0.45
SHS, progression rate (b)[‡*]	0.48 (0-2.28)	0.57 (0.00-2.79)	0.8	0.29 (0-2.12)	0.76 (0-3.33)	0.07
Number of used DMARDs[‡]	2 (1-3)	1 (1-2)	0.02	3 (2-4)	2 (1-4)	<0.01

[†]mean (SD), [‡]median (IQR) *n=543 in EAC-JBI,p[1]=women vs. men EAC-JBI, p[2]= women vs. men BeSt. DAS = disease activity score, HAQ= health assessment questionnaire, SHS= Sharp-van der Heijde score, DMARD = disease modifying anti-rheumatic drugs

Univariable linear regression results showed that females in the EAC-JBI cohort had on average a 0.46 (95% CI: 0.27-0.66) points higher DAS28 than males. A similar pattern was seen in the BeSt cohort (outcome DAS44, beta gender 0.34 (95% CI: 0.15 – 0.54)). After correction for potential confounders at baseline and follow-up time (table 3), the association between female gender and DAS was less strong, but remained statistically significant in both cohorts (EAC-JBI beta 0.32 (95% CI: 0.16 – 0.48); BeSt beta 0.20 (95% CI: 0.02 – 0.37).

While in EAC-JBI female gender was associated with higher HAQ scores beta 1.50 (95% CI: 1.20- 1.88; p<0.01, the back transformed beta means a 1.5 times higher HAQ for women compared to men), no association between gender and HAQ was observed in BeSt (beta = 1.16 (95% CI: 0.88- 1.54) p= 0.29). After correction for potential confounders at baseline and follow-up time (table 4) the association between gender and HAQ remained statistically significant in EAC-JBI, (beta =1.46 (95% CI: 1.17-1.83)), while in the BeSt cohort still no significant association was observed (beta = 0.95 (95% CI: 0.72-1.26)).

No association between gender and the presence/absence of radiographic progression was found in the logistic regression analysis (EAC-JBI: OR = 0.94 (95% CI: 0.66-1.35) and BeSt: OR = 0.70 (95% CI: 0.37 – 1.31)), also not after correcting for potential confounders (Table 5). In all

three models the number of used DMARDs did not alter the association between gender and the outcomes and was therefore omitted from the analyses.

Table 3. Linear regression analysis showing the association between sex and DAS28 / DAS corrected for baseline characteristics and follow-up time

	EAC-JBI			**BeSt study**		
	Beta	**(95%CI)**	**p**	**Beta**	**(95%CI)**	**p**
Sex	0.32	(0.16-0.48)	<0.01	0.20	(0.02-0.37)	0.03
Follow-up time	-0.24	(-0.28; -0.20)	<0.01	-0.28	(-0.35; -0.21)	<0.01
Age	0.01	(0.01-0.17)	<0.01	-	-	-
TJC28	0.05	(0.04- 0.07)	<0.01	-	-	-
Ritchie Articlular Index	-	-	-	0.03	(0.02-0.04)	<0.01
HAQ score	0.29	(0.18-0.40)	<0.01	0.19	(0.05-0.23)	<0.01
ACPA positive	-	-	-	0.19	(0.02-0.36)	0.03
BMI at baseline	-	-	-	0.04	(0.02-0.06)	<0.01

TJC28= tender joint count basen on 28 joints, HAQ= health Assesment Questionaire, ACPA= antibodies to citrullinatedproteins or peptides, BMI= Body Mass Index

Table 4. Linear regression analysis showing the association between gender and HAQ, corrected for baseline characteristics and follow-up time

	EAC-JBI		**BeSt study**	
	Beta (95%CI)	**p**	**Beta (95%CI)**	**p**
Gender	1.46 (1.17-1.83)	<0.01	0.95 (0.72-1.26)	0.71
Follow-up time	0.92 (0.87-0.98)	0.01	0.86 (0.78-0.99)	<0.01
Age	1.01 (1.00-1.02)	<0.01	-	-
Ritchie Articlular Index	-	-	1.05 (1.03-1.07)	<0.01
VAS general health	-	-	1.01 (1.00-1.02)	0.01
DAS28	1.23 (1.11-1.33)	0.01	-	-
CRP	-	-	1.00 (1.00-1.00)	0.32

VAS = visual analogue scale, DAS = disease activity score, CRP = C-reactive protein

Table 5. Logistic regression analysis showing the association between gender and SHS progression yes/no corrected for baseline characteristics

	EAC-JBI			BeSt study		
	OR	**(95%CI)**	**p**	**OR**	**(95%CI)**	**p**
Gender	0.97	(0.61-1.52)	0.88	1.05	(0.48-2.30)	0.91
Age	1.03	(1.01-1.05)	<0.01	1.03	(1.01-1.06)	0.01
Symptom duration	-	-	-	1.01	(1.00-1.02)	0.21
TJC (28 joints)	0.94	(0.89-1.01)	0.07	-	-	-
Ritchie Articlular Index	-	-	-	0.98	(0.93-1.02)	0.32
VAS general health	0.99	(0.98-1.00)	0.05	-	-	-
DAS28	1.38	(0.94-2.02)	0.10	-	-	-
HAQ score	1.19	(0.82-1.73)	0.35	-	-	-
CRP	0.99	(0.99-1.00)	0.05	1.01	(1.00-1.02)	0.05
ACPA positive	1.58	(1.03-2.42)	0.04	4.09	(2.07-8.06)	<0.01
BMI	0.95	(0.91-1.00)	0.04	-	-	-

OR= odds ratio, TJC = tender joint count, VAS = visual analogue scale, DAS = disease activity score, HAQ= health assessment questionnaire, CRP = C-reactive protein, ACPA= antibodies to citrullinated proteins or peptides, BMI= Body Mass Index

Discussion

This report on sex differences in two cohorts of patients with early RA shows a higher disease activity and (in one of the cohorts) functional disability in women compared with men, and comparable radiographic progression for both sexes, whereas DMARD use was higher in women.

The previous finding of a higher disease activity in women was confirmed[5], even after correction for baseline differences between males and females and follow-up time. What causes the difference, when looking at separate components of the DAS? In the present study a trend towards a higher SJC in men was found. Earlier studies found both lower and higher SJC in women versus men, but the difference was generally small.[11,14,18] As women biologically have a higher ESR compared with men[12], a difference in ESR would be expected. However, this result is not found in the present study nor at every follow-up measurement in other studies.[5,11] It may indicate that men with RA have a relatively higher ESR compared with women, indicating more inflammation. TJC and VASGH were both found to be higher in women compared with men, as was reported before.[5,9,11,18] Both differences may at least in part be explained by a lower pain threshold in women.[17] In conclusion, when focusing on the separate components of the DAS score it seems that women mainly score higher on the subjective components of the DAS score.

Functional status tended to be worse for women in one of the cohorts, whereas earlier reports showed a worse functional status in women during two to eight years follow-up.[5,14,15] The absence of a difference in functional status between males and females in the BeSt study may in part be caused by the DAS-steered tight control treatment strategy. Overall, differences in functional status between men and women are difficult to interpret for physiological and psychological reasons, as was clarified in the introduction.

The radiographic progression rate was similar in women and men in the EAC-JBI, while in BeSt a trend was seen with higher rates for men compared with women. In the BeSt study the percentage ACPA positives is higher in men than in women, which is associated with more radiographic progression.[41] In the regression model radiographic progression rate was dichotomised into radiographic status (progression yes or no); no differences between women and men were found, which remained after correction for confounders at baseline. Contradictory results of sex as a prognostic factor for radiographic damage have been reported before. A number of studies with one to eight years of follow-up found similar radiographic progression, or sex was not a prognostic factor.[5,15,20,35,42] Three studies reported that female sex was a predictor for radiographic progression, independent of other risk factors.[30-32] Two of those used the Larsen score[43] instead of SHS,[30,32] which is a less sensitive method in an early stage of the disease, and the third was a cross sectional study.[31] This might explain some of the differences. Therefore, radiographic status does not seem to differ clearly between men and women with RA. However, in order to draw firm conclusions, the intensity of treatment needs to be taken into account.

Irrespective of whether treatment was guided according to the physician's preference (EAC-JBI) or based on DAS measurements (BeSt), women had more frequent treatment changes than men. The number of used DMARDS did not change the association between sex and radiographic progression, but in the EAC-JBI a slight association was found between radiographic progression rate and DMARD use, irrespective of sex [data not shown]. This can be interpreted as consistent with the physician's inclination to use more DMARDs in those patients who have more radiographic progression. In BeSt on the other hand, women have more DMARD use based on a higher disease activity (consistent with the protocol of DAS driven therapy), but men tend to have higher radiographic progression. The higher use of DMARDs in women may compensate for a possible tendency to a more severely damaging disease course in women. To achieve the lowest possible radiographic progression rate, men may need to be treated more intensively than women. As the disease activity is lower on average in men, the cut-off level of the DAS for a change of treatment may need to be set lower in men in the case of a DAS driven treatment setting. In the EAC-JBI cohort, which is based on routine care, the rheumatologists may take other factors into account beside the disease activity, resulting in similar radiographic progression.

In conclusion, women have a higher disease activity, worse functional status and use more medication than men, with the end result of similar scores for the objective outcome parameter of radiographic status. Additional other measures than medication may be needed to lower the higher burden of disease that is experienced by women.

Acknowledgments

We thank dr. A.P.A Prins for scoring part of the radiographs of the EAC-JBI and V. van de Lugt and E. de Wit-Taen for collecting patient data in the EAC-JBI. We would like to thank all rheumatologists and trainee rheumatologists who enrolled patients in the BeSt study, drs. M. Güler-Yüksel for scoring the radiographs of the BeSt study and all research nurses of the participating centers for their contributions.

References

1. Symmons DP, Barrett EM, Bankhead CR, Scott DG, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. Br J Rheumatol 1994;33[8]:735-9.
2. Kvien TK, Uhlig T, Odegard S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci 2006;1069:212-22.
3. van der Heijde DM, van Riel PL, van Rijswijk MH, van De Putte LB. Influence of prognostic features on the final outcome in rheumatoid arthritis: a review of the literature. Semin Arthritis Rheum 1988;17[4]:284-92.
4. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63[9]:1090-5.
5. Ahlmen M, Svensson B, Albertsson K, Forslind K, Hafstrom I. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. Ann Rheum Dis 2010;69[1]:230-3.
6. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, Schreuder GM, Ewals JA, Terwiel JP et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis Rheum 2008;58[5]:1293-8.
7. Combe B. Progression in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2009;23[1]:59-69.
8. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38[1]:44-8.
9. Hakkinen A, Kautiainen H, Hannonen P, Ylinen J, Makinen H, Sokka T. Muscle strength, pain, and disease activity explain individual subdimensions of the Health Assessment Questionnaire disability index, especially in women with rheumatoid arthritis. Ann Rheum Dis 2006;65[1]:30-4.
10. Leeb BF, Andel I, Sautner J, Fassl C, Nothnagl T, Rintelen B. The Disease Activity Score in 28 joints in rheumatoid arthritis and psoriatic arthritis patients. Arthritis Rheum 2007;57[2]:256-60.
11. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther 2009;11[1]:R7.
12. Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. Br Med J (Clin Res Ed) 1983;286[6361]:266.

13. Radovits BJ, Fransen J, van Riel PL, Laan RF. Influence of age and gender on the Disease Activity Score-28 (DAS28) in Rheumatoid Arthritis. Ann Rheum Dis 2007;
Published online first 27 Oct 2007;doi:10.1136/ard.2007.079913.
14. Hallert E, Thyberg I, Hass U, Skargren E, Skogh T. Comparison between women and men with recent onset rheumatoid arthritis of disease activity and functional ability over two years (the TIRA project). Ann Rheum Dis 2003;62[7]:667-70.
15. Hafstrom I, Bala V, Albertsson K, Forslind K, Svensson B. Joint destruction in early rheumatoid arthritis over 8 years is similar in women and men despite apparently higher disease activity and poorer function in women. Ann Rheum Dis 2010.
16. Riley JL 3rd, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 1998;74[2-3]:181-7.
17. Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. Pain 2003;101[3]:259-66.
18. Leeb BF, Haindl PM, Maktari A, Nothnagl T, Rintelen B. Disease activity score-28 values differ considerably depending on patient's pain perception and sex. J Rheumatol 2007;34[12]:2382-7.
19. Kuiper S, van Gestel AM, Swinkels HL, de Boo TM, da Silva JA, van Riel PL. Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis. J Rheumatol 2001;28[8]:1809-16.
20. Tengstrand B, Ahlmen M, Hafstrom I. The influence of sex on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. J Rheumatol 2004;31[2]:214-22.
21. Iikuni N, Sato E, Hoshi M, Inoue E, Taniguchi A, Hara M et al. The influence of sex on patients with rheumatoid arthritis in a large observational cohort. J Rheumatol 2009;36[3]:508-11.
22. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3[3]:305-9.
23. Bijlsma JW, Oude Heuvel CH, Zaalberg A. Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. J Rehab Sciences 1990;3[3]:71-4.
24. Thompson PW and Pegley FS. A comparison of disability measured by the Stanford Health Assessment Questionnaire disability scales (HAQ) in male and female rheumatoid outpatients. Br J Rheumatol 1991;30[4]:298-300.
25. van den Ende CH, Hazes JM, Le Cessie S, Breedveld FC, Dijkmans BA. Discordance between objective and subjective assessment of functional ability of patients with rheumatoid arthritis. Br J Rheumatol 1995;34[10]:951-5.
26. Leeb BF, Andel I, Leder S, Leeb BA, Rintelen B. The patient's perspective and rheumatoid arthritis disease activity indexes. Rheumatology (Oxford) 2005;44[3]:360-5.
27. Hakkinen A, Kautiainen H, Hannonen P, Ylinen J, Arkela-Kautiainen M, Sokka T. Pain and joint mobility explain individual subdimensions of the health assessment questionnaire (HAQ) disability index in patients with rheumatoid arthritis. Ann Rheum Dis 2005;64[1]:59-63.
28. Jawaheer D, Lum RF, Gregersen PK, Criswell LA. Influence of male sex on disease phenotype in familial rheumatoid arthritis. Arthritis Rheum 2006;54[10]:3087-94.
29. Weyand CM, Schmidt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis. Arthritis Rheum 1998;41[5]:817-22.
30. Fex E, Jonsson K, Johnson U, Eberhardt K. Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. Br J Rheumatol 1996;35[11]:1106-15.
31. Belghomari H, Saraux A, Allain J, Guedes C, Youinou P, Le Goff P. Risk factors for radiographic articular destruction of hands and wrists in rheumatoid arthritis. J Rheumatol 1999;26[12]:2534-8.
32. Sanmarti R, Gomez-Centeno A, Ercilla G, Larrosa M, Vinas O, Vazquez I et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clin Rheumatol 2007;26[7]:1111-8.

33. Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. Arthritis Rheum 2001;44[8]:1736-43.
34. Goronzy JJ, Matteson EL, Fulbright JW, Warrington KJ, Chang-Miller A, Hunder GG et al. Prognostic markers of radiographic progression in early rheumatoid arthritis. Arthritis Rheum 2004;50[1]:43-54.
35. Gossec L, Baro-Riba J, Bozonnat MC, Daures JP, Sany J, Eliaou JF et al. Influence of sex on disease severity in patients with rheumatoid arthritis. J Rheumatol 2005;32[8]:1448-51.
36. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31[3]:315-24.
37. Goekoop-Ruiterman YP, Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52[11]:3381-90.
38. van der Heijde DM, van 't Hof M, van Riel PL, van De Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20[3]:579-81.
39. van der Heijde DM. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999;26[3]:743-5.
40. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Güler-Yüksel M, Zwinderman AH, Kerstens PJ et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 2009;68[6]:914-21.
41. Kroot EJ, de Jong BA, van Leeuwen MA, Swinkels H, van den Hoogen FH, van't Hof M et al. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2000;43[8]:1831-5.
42. Sanmarti R, Gomez A, Ercilla G, Gratacos J, Larrosa M, Suris X et al. Radiological progression in early rheumatoid arthritis after DMARDS: a one-year follow-up study in a clinical setting. Rheumatology (Oxford) 2003;42[9]:1044-9.
43. Kirwan JR. Using the Larsen index to assess radiographic progression in rheumatoid arthritis. J Rheumatol 2000;27[1]:264-8.